No. 2017-1480

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

AMGEN INC., AMGEN MANUFACTURING, LTD., AND AMGEN USA, INC.,

Plaintiffs- Appellees,

v.

SANOFI, AVENTISUB LLC, REGENERON PHARMACEUTICALS, INC., AND SANOFI-AVENTIS U.S. LLC.,

Defendants- Appellants.

Appeals from the United States District Court for the District of Delaware in consolidated Case No. 14-CV-1317, Judge Sue L. Robinson.

BRIEF OF *AMICUS CURIAE*
ELI LILLY AND COMPANY.
SUPPORTING DEFENDANTS-APPELLANTS

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February 23, 2017

CERTIFICATE OF INTEREST

Counsel for the *amicus curiae* Eli Lilly and Company certifies the following:

1. The name of every party or *amicus* represented by me is:

Eli Lilly and Company.

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

Eli Lilly and Company.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or *amicus curiae* represented by me are:

None.

4. The names of all law firms and the partners or associates that appeared for the party or *amicus* now represented by me or are expected to appear in this Court are:

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Dated: February 23, 2017

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Eli Lilly and Company ("Lilly") submits this brief as *amicus curiae* in compliance with Rule 29 of Federal Rules of Appellate Procedure and with this Court's Rule 29. Lilly does not have a direct stake in the result of this appeal. The parties to this case have not contributed in any way to the preparation of this brief. The parties have consented to the filing of this brief.

1. STATEMENT OF INTEREST OF *AMICUS CURIAE*

Lilly is a research-based pharmaceutical company that develops and markets innovative medicines. Antibodies, as potential treatments for a diverse set of diseases, make up roughly one-half of Lilly's clinical pipeline. However, patient access to these promising medicines is threatened by patents, like the patents at issue, that claim antibodies not by what they are but instead claim them solely by how they function, *e.g.*, how they bind to their antigen after administration to a patient.[1] Such an approach is contrary to settled law. And, although these patents do not describe *Amicus'* and many other innovators' antibodies, they nevertheless preempt their future development.

[1] Other functional properties typically claimed in these antibody patents include: binding, neutralizing, inhibiting, agonizing, antagonizing, competing with another antibody, binding to or recognizing particular portions of the target molecule (antigen), often referred to as the "epitope," and various quantitative measures of these functions, such as kinetic measures (k_{on} and k_{off}), affinity measures (K_d and K_a), and potency measures (e.g., IC_{50}).

Amicus is an advocate for a robust patent system that incentivizes high risk / high cost drug research. However, functionally defined antibody patents, like those at issue, overreach and are not a prerequisite to develop antibodies; instead these patents discourage, tax, or in the case at issue, prevent such development to the detriment of patients and payers. The written description requirement prevents this overreach. This appeal provides this Court with an excellent opportunity to clarify the application of written description law to antibodies and make clear that the right to exclude competitive antibody innovation must be commensurate in scope with the disclosure of antibodies, not with the disclosure of a "newly-characterized antigen."

II. INTRODUCTION

Antibodies are becoming increasingly important for treating human diseases with the number of novel therapeutic antibody products in medical practice nearly doubling since 2013.[2] Despite the excitement (or maybe because of it), antibody innovation is encumbered by a unique risk not seen in small molecule drug development. This risk stems from patents which, contrary to this Court's

[2] As of March 2012, twenty-seven antibodies were marketed in the US. Janice M. Reichert, *Marketed Therapeutic Antibodies Compendium*, 4 MABS 413 (2012), a list setting forth twenty four antibodies approved since 2012 may be found at: Novel Drugs Summary 2016, U.S. FOOD & DRUG ADMINISTRATION, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm534863.htm (last updated Feb. 21, 2017).

precedents regarding the written description requirement under 35 U.S.C. § 112, claim antibodies solely by their function(s), e.g., by reference to their ability to bind to a naturally occurring biological target (their antigen). Such patents, to the detriment of patients and payers, chill and tax development of unique antibody drug products that act on the same antigen.

Make no mistake - Appellees' ("Amgen") assertion that without such overbroad patents, "No company will expend the resources necessary to bring breakthrough products to market only to have others develop similar products and compete in the marketplace"[3] is demonstrably false. Consider, for example, the multiple statins (cardiovascular disease), anti-TNF agents (autoimmune disease), SSRI inhibitors (depression), SGLT inhibitors (diabetes), and PDE5 inhibitors (erectile dysfunction) that each function against the same target in their respective markets. In fact, Amgen' own EGFR inhibitor Vectibix® (cancer) was developed ***after*** approval of, but targets the same biological target as, Amicus's EGFR inhibitor Erbitux®. Simply put, rather than enable innovation, these overly broad patents enable their holders to monopolize a naturally occurring biological target and thereby preempt an entire therapeutic antibody market from any competition.

Turning to the controversy before this Court, the disputed claims cover a genus of antibodies that bind to a naturally occurring antigen, PCSK9. The claims

[3] Appellees' January 27, 2017 Opposition to Appellant's Motion for a Stay at page 25.

do not recite any structural features of the antibodies *per se* – instead the claims only recite various functional characteristics, *e.g.*, "binds" to PCSK9. As a foundation to all of its proffered evidence that these claims were adequately described, Amgen relied on the so-called "newly-characterized antigen test." Because of its foundational relationship to the written description issues in this case, the "newly-characterized antigen test" is at the core of an unjustifiably unique application of law that threatens innovative antibody drug development.

This Court should reaffirm that purely functional antibody genus claims, like those before this Court, lack written description when their supporting disclosures distinguish the claimed genus solely by what they do rather than by what they are. *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997). Furthermore, unless this Court provides definitive instruction regarding proper application of the written description requirement to functionally-defined antibody claims, and firmly rejects the newly characterized antigen test as a means for complying with the written description requirement, such claims shall continue to improperly tax antibody innovation leading to more uncertainty in a burgeoning area of drug development, more expensive antibody medicines, and delays or removal (as Amgen seek here) of alternative treatment options for patients and payers.

III. ARGUMENT

A. This Court Should Directly Confront and Repudiate the "Newly-Characterized Antigen" Test

This Court should take this opportunity to directly address and reject the so-called "newly-characterized antigen" test which, as described herein, improperly conflates enablement concepts in the context of a test for written description. The newly-characterized antigen test posits that the hypothetical claim "***antibodies*** that bind to antigen X" is adequately described under 35 U.S.C. § 112 when ***antigen X*** is adequately described.[4] This test does not require a description of the claimed composition (the antibodies), but instead requires only a description of unclaimed subject matter (the antigen). As such, the test is inconsistent with § 112's mandate to describe the claimed invention.[5] The test, therefore, is more accurately characterized, and will be referred to hereafter, as the "Antibody Exception".

Judicial review and repudiation of the Antibody Exception is appropriate for at least two reasons. First, as discussed in Section A.1. below, the rational for the Antibody Exception is that an antibody claimed by reference to its described antigen is enabled. That rationale, by itself, is inconsistent with this Court's precedent in *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336 (Fed. Cir. 2010) (en banc), which reaffirmed that satisfying the enablement requirement under 35 U.S.C. § 112, 1st paragraph involves a different inquiry than that for written description. Second, as discussed in Section A.2. below, to the extent this Court has considered the Antibody Exception, it has done so in cases where the exception was not at issue. Therefore, contrary to Amgen's assertions, this Court has not endorsed the Antibody Exception as binding precedent.

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[4] *Written Description Training Materials, Revision 1*, UNITED STATES PATENT AND TRADEMARK OFFICE (March 25, 2008), https://www.uspto.gov/sites/default/files/web/menu/written.pdf.

[5] Due to the degeneracy of the genetic code, the amino acid sequence of PCSK9 discloses the genus of DNA "encoding" PCSK9, but no such correlation (antibody code) exists between an antigen and its antibodies. Thus, although a claim to "DNA encoding PSCK9" is described by PCSK9, PCSK9 does NOT describe "Antibodies that bind PCSK9."

In any event, clarification is needed: the District Court Judge in this case tentatively expressed that applying the Antibody Exception to the claims at issue was "probably the law." Appx1452(1268:22). Further, at the time of granting Amgen' request for a jury instruction on the Antibody Exception, the judge stated, "[w]ith respect to written description…the contours of the law under the circumstances of this case…are not easily defined." Appx1449(1256:11-13). Given the uncertainty expressed by the court below, this Court should directly address and repudiate the Antibody Exception.

1. The Antibody Exception Is Contrary to Precedent Construing 35 U.S.C. § 112(a)'s Mandate to Provide a Written Description.

The Antibody Exception traces its roots to training materials created by the United States Patent and Trademark Office ("PTO") which were first published in 2000, that were revised and republished in 2008, and that have since been withdrawn[6] ("Training Materials"). The Training Materials were used by PTO patent examiners to implement separately promulgated, "Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶1, 'Written Description' Requirement" [7] ("Guidelines"). The Guidelines set forth relevant law and analytical frameworks to be used by PTO patent examiners as they evaluate whether claims before them have been adequately described under existing written description law. The Training Materials, on the other hand, set forth various hypothetical fact patterns and claims ("Examples") to illustrate how the Guidelines' analytical frameworks might be applied by the PTO examiners.

Example 13 of the Training Materials,[8] previously referred to by this Court as the "PTO's antibody example,"[9] sets forth the Antibody Exception and rationalizes it based on a view that "production of antibodies against a well-characterized antigen was conventional," that methods "of making [and preparing] antigen-specific antibodies" were "routine [and not difficult]," and that "antibody technology was well developed and mature."[10] Paraphrasing, Example 13 thus stands for the proposition that, so long as the claim is enabled, the claim is described. This is the essence of the Antibody Exception.

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[6] First published in Feb. 28, 2000 (*Revised Interim Written Description Guidelines Training Materials*, UNITED STATES PATENT AND TRADEMARK OFFICE, https://www.uspto.gov/web/offices/pac/writtendescription.pdf (last visited Feb. 21, 2017), and then later, in March 2008, the training materials were revised and republished as Written Description Training Materials, Revision 1, March 25, 2008 (https://www.uspto.gov/sites/default/files/web/menu/written.pdf (last visited Feb. 20, 2017)). The PTO now notes that the Training Materials have been "archived" and that "[a] new version will be prepared to reflect changes in the law since 2008, including any required clarifications due to developments in the law relating to 35 U.S.C. 112." *Examination Guidance and Training Materials*, UNITED STATES PATENT AND TRADEMARK OFFICE, https://www.uspto.gov/patent/laws-and-regulations/examination-policy/examination-guidance-and-training-materials (last modified Jan. 5, 2017).

[7] Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, "Written Description" Requirement, 66 Fed. Reg. 1099 (Jan. 5, 2001).

[8] Example 13 in the 2008 Guidelines corresponds to Example16 in the original year 2000 version.

However, the Antibody Exception contradicts this Court's jurisprudence relating to written description for genus claims. For example, two years after the Training Materials were republished, this Court reaffirmed in *Ariad* that the requirement for a written description is separate from the enablement requirement and that written description for a genus claim must allow identification of claimed from unclaimed subject matter by something other than a recited function. *Ariad*, 598 F.3d at 1341. Yet, the Antibody Exception requires only enablement, which according to *Ariad*, is insufficient by itself for genus claims like those before this

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[9] *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1352 (Fed. Cir. 2011).

[10] *Written Description Training Materials, Revision 1,* UNITED STATES PATENT AND TRADEMARK OFFICE (March 25, 2008), https://www.uspto.gov/sites/default/files/web/menu/written.pdf.

Court.[11] In addition, this Court long ago held in *Fiers v Revel*, 984 F.2d 1164, 1169 (Fed. Cir. 1993) that:

> []Irrespective of the complexity or simplicity of the method of isolation employed, conception of a DNA, **like conception of any chemical substance**, requires a definition of that substance **other than by its functional utility**. (Emphasis added).

The Antibody Exception's incongruence with this Court's written description jurisprudence was illustrated recently in *Abbvie Deutschland GmbH v. Janssen Biotech, Inc.*, 759 F.3d 1285 (Fed. Cir. 2014) where this Court set forth and applied the technology-agnostic written description law to functionally-claimed *antibodies*:

> [A] sufficient description of a genus . . . requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus **so that one of skill in the art can visualize or recognize the members of the genus**.
>
> …
>
> [F]unctionally defined claims can meet the written description requirement **if a reasonable structure-function correlation is established**, whether by the inventor as described in the specification or known in the art at the time of the filing date.

[11] *Ariad* 598 F.3d at 1348 (rejecting the argument that written description was satisfied because one of skill in the art "would be enabled to make [the claimed invention]….").

Abbvie, 759 F.3d at 1299, 1301 (quoting *Eli Lilly*, 119 F.3d at 1568–69; citing *Enzo Biochem, Inc. v. Gen–Probe Inc.*, 323 F.3d 956, 964 (Fed.Cir.2002)) (Citations and internal quotations omitted, emphasis added).

As the Antibody Exception does not derive from disclosure of either "representative … species" or "common structural features" of the claimed antibodies, this Court's analysis of the Antibody Exception should focus on whether a known or disclosed "structure-function correlation" supports the exception. Contrary to assertions made by Amgen, there is no known or disclosed correlation between an antibody's structure and its functional ability to bind an antigen that would allow one to **visualize or recognize the** claimed from unclaimed antibodies. In fact, the experts for both parties in this case agreed that **antibody structure** cannot be determined from a recited antibody **function**, *e.g.*, binding PCSK9.

> Amgen's Direct Examination of Dr. Petsko:
>
> Q. Okay. So if you recall, Drs. Eck and Siegel said, well, just because Amgen disclosed the sweet spot on PCSK9, that does not tell you enough about antibodies that would bind there. You can't sit at your desk and write out the sequences. I think they said you can't predict. Do you have an opinion about that?
>
> A. My opinion is that they're right. ….

Appx1314(836:5-11).

With no known function / structure relationship between antibodies and their function (binding to a specified antigen) that would allow the public to distinguish claimed antibodies from unclaimed antibodies, the alleged enablement of a claim that recites "antibodies that bind antigen X" does not rescue its missing description. Moreover, embedded in this Court's statements setting forth the written description requirement are several policy objectives that are undermined by the Antibody Exception. For example, in *Ariad* this Court explained that adherence to written description ensures the public has been placed in "possession of the claimed subject matter…." *Ariad*, 595 F.3d at 1351. By requiring the applicant to describe the claimed invention, this Court has explained the public is put on "notice of the boundaries" of that which has been excluded from the public domain. *Id*. at 1347. When claims set forth only functional limitations (without a known or disclosed function/structure relationship), the public is left to conduct research to actually invent the claimed subject matter. Thus, the Antibody Exception "is not consistent with the statute or the policy behind the statute, which is to promote disclosure of inventions, not of research plans." *Fiers*, 984 F.2d at 1169. This Court should repudiate the Antibody Exception as being legally insufficient to meet 35 U.S.C. § 112(a)'s written description requirement.

2. The Antibody Exception Has Never Been Squarely Before This Court.

This Court first considered the Antibody Exception as embodied in the Training Materials in *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956 (Fed. Cir. 2002). In that case, the patent claims were directed to nucleotide sequences that hybridize selectively to gonorrhea DNA over meningitides DNA. The patent specification did not set forth any gonorrhea or meningitides DNA sequences, but the patentee deposited several such sequences at the American Type Culture Collection (ATCC). The district court held by summary judgment that the deposited sequences were not adequate to describe the claimed genus of nucleotides that hybridize to the deposited DNA and, therefore, the claimed genus of nucleotides lacked written description support. *Enzo*, 323 F.3d at 960-62.

This Court, however, disagreed and held that the deposited DNA with the ATCC was an adequate written description of those sequences. *Id*. at 966. This Court also considered "whether the description requirement is met for all of the claims on the basis of the functional ability of the claimed nucleotide sequences to hybridize to [DNA] strains of … gonorrhoeae that are accessible by deposit." *Id*. at 964. Rather than deciding that issue as a matter of law by relying on the Training Materials, this Court remanded the case to the district court stating:

> On remand, the court should consider whether one of skill in the art would find the generically claimed sequences described on the basis of Enzo's disclosure of the hybridization function and an accessible structure, consistent with the PTO **Guidelines**.

Id. at 966 (emphasis added).

Four things are important to understand about *Enzo* : (1) even after considering the hybridization example set forth in the interim Training Materials, which was brought to the attention of that Court[12] and that would have found the claims adequately described, this Court recognized that the existence of an applicable function / structure relationship was a matter of debatable fact and remanded that issue to the district court; (2) the existence of a function / structure relationship between an antigen and its antibodies as it may pertain to written description of an antibody claim was not at issue, *i.e.*, the veracity of the PTO's positions on antigens and their antibodies as set forth in the Training Materials was not vetted; (3) consequently this Court did not (and could not) hold that the PTO's factual underpinnings and conclusions regarding antigens and their antibodies were correct as a matter of law; and (4) in any event, the **Guidelines** which set forth analytical frameworks were explicitly adopted – the interim **Training Materials** which applied those frameworks to specific fact patterns were not. Thus, any direct or indirect reliance by Amgen on *Enzo* to support their antibody claims' compliance with written description precedent is clearly misplaced.

[12] Brief for Defendants-Appellees at 55-56, *Enzo Biochem, Inc. v. Gen–Probe Inc.*, 323 F.3d 956, 964 (Fed.Cir.2002) (No. 01-1230) (citing to "Example 9" in the interim Training Materials).

After *Enzo*, this Court had the occasion to apply the Antibody Exception in *Noelle v. Lederman*, 355 F.3d 1343 (Fed. Cir. 2004), an appeal of a PTO interference proceeding. However, as with *Enzo*, the Antibody Exception's merit was not at issue. In *Noelle*, both litigants pursued broad antibody claims based solely on an alleged description of an antigen and the issue those litigants presented to this Court was, as between Noelle and Lederman, who was first to possess and describe the relevant antigen? In that context, both litigants sought to rely on the Antibody Exception to demonstrate compliance with the written description requirement and neither party challenged its appropriateness *ab initio*.

Thus, Lederman argued:

> In particular, … the [interim Training Materials] makes plain that, **when an antigen has been isolated and purified,** a claim to an antibody that binds to it is appropriate…. (Emphasis in original).

Brief of Appellees at 33-34, *Noelle v. Lederman*, 355 F.3d 1343 (Fed. Cir. 2004) (No. 02-1187). Whereas Noelle argued:

> In its recent decision in [Enzo] the Court … referred to the [interim Training Materials] **for its conclusion** that a claim to "an isolated antibody capable of binding to antigen X" is sufficient for § 112, paragraph one, compliance …." (Emphasis added).

Brief for Appellant at 34, *Noelle* 355 F.3d (No. 02-1187). Contrary to the assertions made in the appeal briefs filed in *Noelle*, this Court did not "conclude" in *Enzo* that a claim to "an isolated antibody capable of binding to antigen X" is sufficient for 35 U.S.C. § 112 compliance. Moreover, given that the claims in *Enzo* and the disclosure supporting same were directed to nucleotide sequences that hybridize to DNA, any position this Court allegedly took in *Enzo* and *Noelle* on antibody written description was clearly dicta. The case before this Court, with adversarial counsel representing opposing parties, for the first time squarely presents the Antibody Exception's merit to this Court for review.

With the debate properly framed and before this Court for the first time, this Court should reject the Antibody Exception as clearly in violation of this Court's precedents construing the written description requirement.

B. This Court Should Reject the Antibody Exception and the Significant Enlargement of the Antibody Exception Appellees Seek

Should this Court decline this opportunity to directly address and repudiate the Antibody Exception, this Court should reject the significant expansion of the exception's scope advanced by Amgen.

Amgen seeks to expand the already suspect Antibody Exception in two ways. First, Amgen seeks to expand "new antigen" to include one or more particular amino acids of a new or old (previously characterized) antigen, thus reading-out even an expectation that the antigen be "new." *See Centocor v. Abbott*, 636 F.3d 1341, 1352 (Fed. Cir. 2011) (stating that "[w]hile our precedent suggests that written description for certain antibody claims can be satisfied by disclosing a well-characterized antigen, **that reasoning applies to disclosure of**

newly characterized antigens ….") (Emphasis added). Thus, under Amgen's proffered construction, that which was old becomes new again. Second, Amgen seeks to incorporate additional distinct functional attributes (e.g., "blocking") within the scope of the Antibody Exception, thereby *expanding* it, to find written description for a subgenus of antibodies which "bind to" a specific residue of a previously characterized antigen ***and*** which also "block" binding of the antigen to its receptor. These expansions are not supported by this Court's written description precedent, including *Noelle*, and are not even supported by the Training Materials.

To support its proffer of a broader Antibody Exception, Amgen relies on Example 13 in the Training Materials and point to this Court's reference to the interim Training Materials in *Noelle*. Appx1452(1269:16-18). However, neither Example 13 nor this Court's discussion of the interim Training Materials in *Noelle* support expansion of the Antibody Exception to the claims at issue. Ignoring for the moment *Amicus*' view that the conclusions set forth in the PTO's Training Materials regarding antibody written description are incorrect, those conclusions are based on the propositions that *making* antibodies to an antigen was "conventional" and "routine."[13] To support those contentions, the Training

[13] *Written Description Training Materials, Revision 1*, UNITED STATES PATENT AND TRADEMARK OFFICE (March 25, 2008) at 46, https://www.uspto.gov/sites/default/files/web/menu/written.pdf.

Materials cite a single reference, Structural Concepts in Immunology and Immunochemistry, 2nd Ed, ("Kabat"), which states that "[n]o difficulties were encountered in preparing antibodies to protein antigens" through "immuniz[ing] the [host] animal … **with …the antigen**." *Id*. at 45 (emphasis added). Even if generating antibodies that bind to one of fifteen specific amino acids out of the 692 amino acids comprising PCSK9 was conventional (and it is not), nothing in the Training Materials evidences the proposition that it is "conventional" or "routine" to make such specific amino acid-binding antibodies which ***also*** possess additional functional attributes such as "blocking" the antigen's interaction with its receptor. Thus, Amgen's reliance on the Training Materials as support for the proffered extension of the Antibody Exception to the claims at issue is clearly misplaced.

Moreover, whatever *Noelle's* alleged precedential relevance may be to the Antibody Exception *per se*, this Court has already rejected its expansion in *Centocor*. In *Centocor*, this Court rebuffed the argument that the Antibody Exception should apply to a claim over a "class of antibodies…hav[ing] desirable therapeutic properties," stating that such a view requires "an unduly broad characterization of the [Training Materials] and [*Noelle*]." *Centocor*, 636 F.3d at 1351-52. Additionally, in *Centocor*, this Court stated that the reasoning set forth in *Noelle* and the Training Materials, if it were to apply at all, would be "where creation of the claimed antibodies is routine," and not in a situation, as here, where generating antibodies possessing at least two discrete functional properties (e.g., binding a specific residue ***and*** possessing a "blocking" function) was neither "conventional [nor] routine." *Id*. at 1352. Thus, this Court has already rejected an argument that *Noelle* endorses the expansion of the Antibody Exception Amgen seeks and should do so again here.

Nevertheless, Amgen argues that their claimed monopoly is appropriate because they have newly described an "epitope", *i.e*., region, of the previously characterized PCSK9 antigen that is important to a known function of PCSK9. However, the alleged non-obviousness of the epitope *per se* under 35 U.S.C. § 103 does not relieve a patentee from their obligation to provide a written description of the claimed antibodies under 35 U.S.C. § 112. Moreover, Amgen's claims do not require the antibodies to bind to the described epitope, but instead require binding only to a **single** residue within the described epitope. And in any event, it is undisputed here that one could not predict which antibodies bind an antigen, much less those antibodies that will both bind to a specific residue ***and*** possess a distinct "blocking" function. Even in the face of this unpredictability, Amgen asks this Court to endorse the claims at issue as being properly described so long as the patent selects and "well characterizes" at least one amino acid of a previously known antigen; such position has no basis in the patent statute, science, the Training Materials, this Court's precedent, or common sense.

In summary, this Court should repudiate the Antibody Exception as contrary to the statutory mandate that a patent disclose a written description of the invention and as inconsistent with this Court's written description precedent. Should this Court decline to repudiate this non-statutory exception to written description, this Court should reject the significant expansion of its scope as proffered by Amgen.

C. Appellees' Disclosure Fails to Provide either a Representative Number of Antibodies falling within the Scope of the Genus, or Structural Features Common to Members of the Genus, Sufficient to Distinguish the Genus *Claimed* from other Antibodies

This Court's decision in *Lilly* remains the seminal authority for application of the written description requirement to chemical genus claims involving biological materials.

> In claims to genetic material . . . a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA,' without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, **visualize or recognize the identity of the members of the genus.**

Lilly, 119 F.3d at 1568 (emphasis added). Thus, Lilly stands for the proposition that description of a genus may be made by recitation of "representative" species falling within the scope of the genus **or** by recitation of "structural features common to the members of the genus." *Id*. at 1569.

While often expressed in terms of distinct "tests," there is really only one standard: to demonstrate possession of the invention, the members of the genus must be recognizable by their "structure, formula, chemical name, physical properties, or other properties of species falling within the genus sufficient to distinguish the genus from other materials." *Ariad*, 598 F.3d at 1350 (citing *Lilly*, 119 F.3d at 1568). In a series of opinions evaluating chemical genus claims defined purely by function for sufficiency under the written description requirement, this Court has repeatedly emphasized the importance of the disclosure of structure, or some correlation to the structure, of the genus being claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916 (Fed. Cir. 2004) (COX-2 enzyme inhibitors not described though structure of COX-2 enzyme was known); *Ariad*, 598 F.3d at 1357 (no descriptive link between the table of decoy molecule sequences and reducing NF-KB activity); *Centocor*, 636 F.3d at 1349-50 (disclosure only provided amino acid sequence for a single mouse antibody variable region which was 'very different' from human antibody variable regions); *Abbvie* 759 F.3d at 1300 (disclosure described only structurally similar antibodies that were not representative of the structure of allegedly infringing product).

In the case before this Court, Amgen has failed to disclose species representative of the structural variation of the antibody genus claimed and have further failed to disclose common structural features shared by the members of the genus, in either case so as to distinguish the claimed antibodies from other antibody compositions. Thus, under controlling precedent, this Court should find Amgen's claims invalid for lack of sufficient written description under 35 U.S.C. § 112(a).

1. **The Size of Appellees' Claimed Genus is Indeterminate, Therefore Assessment of Representation is Futile.**

Genus claims that are defined solely by function in the chemical arts are inherently vulnerable to a finding of lack of written description where it is difficult to predict what would be covered by the claims. *Abbvie*, 759 F.3d at 1301. Regarding genus claims to chemical compounds, this Court in *Lilly* stated:

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus.

Lilly, 119 F.3d at 1568.

The claims at issue clearly do not involve generic formulae. And the experts in this case agreed that one of skill in the art cannot visualize or recognize the identity of the members of the claimed genus from their disclosed functions. Appx1307(808:24-809:12). As such, the "outer boundary" of the claimed genus is unknown, both in terms of size and structural diversity, and neither Amgen's disclosure, nor the knowledge in the art, allows the skilled artisan to predict the undisclosed members of the genus. And since one can not predict the structure of antibodies falling within the scope of the genus, assessment of "representation" is futile. To put it in mathematical terms, when one doesn't have any information about the denominator for a given fraction, the numerator is meaningless.

2. Appellees' Disclosure Fails to Reflect the Diversity in Structure of the Claimed Genus of Antibodies Foreclosing Representation by the Disclosed Antibodies.

Moving to evidence of representation actually proferred by Amgen in this case, Amgen's specification provided structural identifying information for twenty-four distinct antibody species. Among this group, only two antibodies, 21B12 and 31H4, were definitively characterized for "binding" to the residues on PCSK9 as required by the claims. And of the other twenty-two disclosed antibodies, eleven have "essentially the same" sequences as 21B12. Appx1243(558:12-19). Nonetheless, Amgen argues that the 21B12 and 31H4 antibodies are in fact representative of the species covered by the claims. In response to whether he had an opinion as to whether the 21B12 and 31H4 antibodies were representative (of the species covered by the claims), Amgen's expert testified: "[Y]es. . . they give me all the information I need to **define the part of . . . PCSK9**, where the antibodies **need to bind** in order to block." Appx1306(807:1-3)(emphasis added)). According to Amgen's expert, the 21B12 and 31H4 antibodies left different "footprints" on opposite sides of the claimed region on PCSK9 and if one were to draw a line around these regions one would "cover the sweet spot virtually perfectly." Appx1306(806:18-20). In other words, Amgen semingly argued that because they had disclosed antibodies having diverse "footprints," that together covered the antigen residues recited in their claims, they had disclosed species "representative" of the genus of antibodies claimed. This argument is simply a repackaging of the Antibody Exception; asserting that disclosure of antibodies with the **function of binding recited antigen residues** provides "representation" across the full scope of the claimed genus of **antibody structures**.

Furthermore, Amgen's argument is at odds with this Court's precedents including its recent decision in *AbbVie*. In *Abbvie*, this Court made clear that disclosure of the claimed genus' **structural diversity**, not merely diversity in the **functional limitation**, is required. There, the patentee argued that the disclosed antibodies reflected the variation of the claimed genus because they covered the "range of the claimed feature, the K*off* rate." This Court however, disagreed:

> The K_{off} rate is merely a desired result, rather than the actual means for achieving that result. The asserted claims are directed to new compositions . . . human antibodies having desired IL-12 binding characteristics. It is undisputed that the structure of the antibody determines its antigen binding characteristic. In order to demonstrate that it has invented what is claimed, AbbVie's patents must adequately describe representative antibodies to reflect the structural diversity of the claimed genus.

Abbvie, 759 F.3d at 1301. Like the disclosure in *Abbvie,* Amgen's disclosure of binding to the recited residues on PCSK9 is only an indication of a useful result. It is not an identification of the structural diversity of the species claimed, i.e, *what* "achieves the claimed result." *Id.* at 1299. Rather than disclosing the "full scope" of species representative of the diversity in antibody structures that satisfy the functional limits of the claims, Amgen's patent disclosure amounts to no more than a trial and error approach for identifying such species. Such a disclosure (or lack thereof), fails to comport with the purpose of the written description requirement as expressly held by this Court. *See Lilly*, 119 F.3d at 1568 (stating that "[t]he [written] description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention."); *Ariad*, 598 F.3d at 1353 (citing *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916 (Fed. Cir. 2004) (quoting *Brenner v. Manson*, 383 U.S. 519, 536 (1966)) (A "patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.").

As such, this Court should find that Amgen's claims are not described as a matter of law and should clarify that description, via representative antibody examples, requires disclosure of the structural diversity of the genus of antibodies claimed; not mere disclosure of (one or two) antibodies which bind specified residues of an antigen.

3. Structural Features of the Antigen Provide No Correlation to Common Structural Features of the Antibody Genus *Claimed*.

Amgen's disclosure does not set forth any common structural features of the claimed genus of antibodies that would allow one to distinguish claimed from unclaimed antibodies. Just like all of Amgen's other written description evidence, the structural feature relied upon as "common" to describe the claimed **antibodies** is that of the unclaimed **antigen**. Such a description is legally insufficient under *Lilly* and this Court's precedents.

Much like the DNA sequences at issue in *Lilly*, antibodies generally share a common three-dimensional shape often referred to as a "Y." At the distal end of each "arm" of the "Y," the typical antibody has six complementarity determining regions, or "CDRs" that primarily influence the binding of an antibody to an antigen. However, unlike DNA sequences (*i.e.*, genes) that encode a given protein sequence, the CDR sequences that bind a given antigen cannot be determined based on the antigen sequence. Since each CDR can comprise, on average, ten or more amino acid residues, with each residue being one of twenty different amino acids, the variety of CDR sequence combinations for antibodies that bind a given antigen is extremely diverse.[14]

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[14] For example, to understand just the potential variability within human antibody CDR regions alone, consider that any given human antibody will have six CDRs, each CDR comprising approximately ten amino acid residues. With twenty naturally occurring amino acids, the potential size of the CDR variation, of just human antibodies within this indeterminate genus, is 20^{60}. This does not even consider the potential variation with the variable and constant regions of human

The evidence proffered by Amgen of the common structural features of the *target* being bound by the claimed antibodies is irrelevant to the subject matter claimed – a disclosure setting forth the common *antibody structure* capable of binding and blocking the target is what matters. Amgen attempts to evidence description of the antibodies by analogizing the backbone of a polypeptide chain to a “bracelet”, with the individual amino acid side chains merely reflecting the “charms” or “fine” detail of the bracelet. Removing the “charms” or side chains from the PCSK9 residues reveals a three-dimensional surface on PCSK9 that all antibodies within the claimed genus must fit – in other words, all antibodies within the claims will “shape fit” or be a “structural complement” to the surface defined by the designated residues on PCSK9. Appx1330(902:6-14). Amgen’s specification, however, fails to provide any of the amino sequences common to the *claimed antibodies* that yield the ‘shape fit’ or the ‘structural complement’ to the designated PCSK9 residues.

The only commonality of structure disclosed whatsoever in Amgen’s patent relates to **unclaimed subject matter**, *i.e*, a defined area on PCSK9 *to which* the claimed antibodies must bind. That all antibodies within the genus must have a complementary surface that interacts or “shape fits” with this defined area merely reflects a necessary truism of the functionally defined-claims - not a structural

antibodies, let alone the variation within antibodies of non-human origin which are ***all*** encompassed by the claimed genus.

feature sufficient to distinguish the claimed antibody genus from other antibodies targeting a different region of PCSK9, or even a different antigen altogether.

Just as the claims at issue in *Lilly* failed to define any of the genes (*i.e.*, *nucleotide sequences* encoding the complete human insulin protein) that fell within the claimed genus, Amgen's claims likewise fail to define the *amino acid sequences* shared by the members of the genus that allow them to "bind" the designated residues, and "block" the interaction of PCSK9 with its receptor "LDL-R." As Amgen described no common amino acid sequences for the antibody CDRs that impart the claimed functions to the antibodies within the claimed genus, Amgen's description of an area within PCSK9 is plainly insufficient to know or predict any common structure features of the claimed antibodies. Thus, Amgen's claims are not described via common structural features.

In the absence, such as in this case, of a relevant structure / function relationship, this Court should clarify that satisfaction of the written description requirement for an antibody genus claim by way of "common structural features" must be via disclosure of the structural features common to the claimed material that allows one to distinguish claimed from unclaimed antibodies. That the antibodies are all "shaped like Y's" is clearly not sufficient – claimed and unclaimed antibodies possess that shape. This Court should find, as a matter of law, that the claims at issue are not described via common structural features.

IV. CONCLUSION

This appeal provides this Court with an excellent opportunity to directly address, and squarely reject, the Antibody Exception as being inconsistent with 35 U.S.C. § 112(a) and this Court's precedent. Even if this Court declines to address the Antibody Exception in total, this Court should reject the enlargement of its scope advanced by Amgen as lacking basis in the rationale undergirding the Antibody Exception and as having been already denied by this Court in *Centocor*. Finally, because the functionally-defined genus claims at issue are not supported by a disclosure of a representation of the scope of, or structural feature common to, the genus, the public has not been placed in possession of the full scope of the genus. Thus, this Court should invalidate these claims for want of written description.

Furthermore, it is important for this Court to appreciate that the field of antibody engineering remains an unpredictable art; one is not able to predict the structural identity of antibodies that bind a protein target (antigen) based on the structure of the target (and likewise, knowing the structure of an antibody does not allow the skilled artisan to predict the protein target that it will bind). If this Court affirms Amgen's approach, the Antibody Exception becomes the rule **but only in the antibody arts** –rendering the standard first articulated by this Court in *Lilly* superfluous and tearing the policy considerations for a written description in the antibody arts to shreds. All newly characterized antigens (and epitopes of antigens) will inherently describe the genera of their antibodies thus obviating the need for patentees to disclose either representative species or common structural features of their claimed genus. Antibody patentees will no longer be required to provide the public meaningful disclosure that would form the basis of improvements to the patentee's antibody discoveries and that would put the public on notice of what constitutes an infringing act. For these reasons, this Court should reject Amgen's approach to claiming antibodies and clarify the already articulated technology-agnostic standards for determining compliance with written description.

CERTIFICATE OF COMPLIANCE WITH RULE 32

1. I certify that this brief complies with the type-volume limitations of Fed. R. App. P. 32(a)(7)(B). According to the word-processing system used to prepare it, this brief contains 6,732 words, excluding the parts exempted by Fed. R. App. P. 32(f) and Fed. Cir. R. 32(b).
2. I certify that this brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6) by using Microsoft Office Word in Times New Roman 14 point font.

Date: February 23, 2017

Respectfully submitted,

/s/ Duane C. Marks
Duane C. Marks

CERTIFICATE OF SERVICE

I hereby certify that on February 23, 2017, I electronically filed the foregoing with the Clerk of the Court for the United States Court of Appeals for the Federal Circuit by using the CM/ECF system. I certify that all participants in this case are registered CM/ECF users and that service will be accomplished by the CM/ECF system.

Date: February 23, 2017

s/ Duane C. Marks
Duane C. Marks